The optical density at 450 mμ above the baseline is used to predict the severity of haemolytic disease in the foetus, and 193 out of 252 predictions were correct. The diazo test gave the correct result in a further 23 patients. Seventeen infants were lost as a result of haemolytic disease (7%).

It is concluded that liquor examination is of definite value in the prediction of severity of haemolytic disease, and in determining the subsequent management of the patients.

I am grateful to Professor R. J. Kellar and Dr. G. D. Matthew for their help and encouragement during this investigation. I am also grateful to the consultant obstetricians in the South-Eastern Region of Scotland for permitting me to obtain liquor from their patients. I also wish to express my thanks to Miss J. Cameron, A.M.I.L.T., for her assistance in devising the diazo liquor test; to the technicians in the clinical laboratory of the Simpson Maternity Hospital for testing the liquor; and to Sister M. Isdale, of the Simpson Maternity Hospital, for her help in carrying out the tests and in the investigation of the patients. The co-operation of Dr. R. A. Cumming and the staff of the Regional Blood Transfusion Centre and of the paediatricians attached to the Simpson Maternity Hospital has been invaluable. This material forms part of a thesis for the degree of Doctor of Medicine accepted by the University of Edinburgh.

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Hand Eczema

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When eczema affects the hands it tends to be disabling as well as uncomfortable; to the patient it is ever before him, inescapable; it embarrasses him because it is so often easily visible to others; and it is common.

The 106 cases of hand eczema which form the basis of this report were in patients seen by me for the first time over a period of 12 months and represent, therefore, about 5% of all patients attending the dermatological out-patient clinic. Even so, they are selected, since they are only those cases where the hands were originally involved and in which the hand lesion was the primary complaint. Other eczemas, where the hands were later involved as a part of a more widespread eruption, have not been included and would, no doubt, have provided a further substantial number. All the patients in the present series were seen, investigated, and treated by me personally with the main object of forming a consistent assessment of causative factors and of the value of treatment. Final review was carried out 18 to 24 months after first attendance; seven failed to report for follow-up.

The group contained 56 men and 50 women, a slight difference of no likely significance. The age at onset (Table I)

TABLE I.—*Age at Onset of Hand Eczema*

Age (yrs)	-5	-10	-15	-20	-25	-30	-35	-40	-45	-50	-55	-60	-65	-70	Total
Men ..	1	1	—	3	6	3	4	7	4	11	7	4	2	3	56
Women ..	—	2	3	5	7	4	4	5	4	7	5	2	2	—	50

shows a difference in the sexes. In men a peak incidence is found at 46–50 years of age, while in women the age distribution is more level from 16 years onwards; this might be attributed to the effect of housework with its cleansers and primary irritants, but for reasons given below this suggestion cannot be substantiated.

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Clinical Groups

Among the whole series it is possible to define certain clinical groups.

Nummular Eczema

The term "nummular" is applied to a type of discoid eczema, usually affecting the backs of the hands and fingers, sometimes the forearms, in which the eczematous areas are well outlined with normal skin between. There were 12 men and four women showing this pattern, one case being possibly atopic. None gave positive reactions to routine patch tests.

This group was distinguished by its relatively short duration, often clearing up in the course of some months.

Nickel Allergy

Calnan and Wells (1956) drew attention to the fact that nickel is a very common cause of epidermal allergy in women in the United Kingdom. They pointed out, too, that these patients are prone to hand eczema even after nickel dermatitis has healed and without identifiable continuing contact with nickel. Six women in the present series were of this kind. All of them knew of their proneness to metal rashes and avoided contact with metals. The duration of their hand eczema was from one month to three years, but nickel sensitivity was of many years' duration.

Nickel sensitivity in men is more often occupational, occurring, for example, in electroplaters. Two men in the present group were found on patch-testing to be nickel-sensitive; one of these gave a history of a rash beneath a wrist-

watch, but in the other it was unexplained. In neither of these men had there been occupational exposure to nickel.

Atopy

It is common for atopic eczema to involve the hands, but unusual for it to present primarily as hand eczema. The diagnosis then rests on a previous history of skin disease and associations with asthma or hay-fever either in the patient or in relatives. Five cases in the present series were deemed to be of this kind. The hand lesion was a patchy papular eczema involving mainly the dorsal surfaces, sometimes with weeping. It was not objectively distinguishable from other types of hand eczema.

Hyperkeratotic Dermatitis of the Palms

By this name Sutton (1956) refers to a lesion which usually appears only on the palms as well-demarcated areas covered with fine adherent scales and tending to produce fissures in the skin creases. Vesicles and weeping do not occur and there is little or no erythema. The lesion tends to be static and it comes mostly in middle age. Although local applications may produce substantial improvement, it reappears within a day or two if treatment is stopped. Some dermatologists regard this as a neurodermatitis, a name which I hesitate to use in the absence of itching. Others maintain that most of these cases are really psoriasis. Although included in this series I doubt whether they are truly eczematous.

In the present series five men and four women showed these lesions. One of the women later developed characteristic lesions of psoriasis; one of the men turned out to be sensitive to orange-peel and recovered after eliminating this contact. The rest remained inscrutable, and, except for one, persistent.

Post-partum

The onset of hand eczema in women shortly after childbirth is usually attributed to increased exposure to detergents. This explanation may not always be true, for I have seen this occur in women who had no domestic work to do. An endocrine and psychological factor are possible alternatives.

Of three such cases in the present series, the eruption came on the day following delivery in one; in the others it was delayed two weeks and three months.

Tinea

In only one case was fungus found on the hand. This was a relapsing hand eczema in which the feet also were involved. The well-known association between hand eczema and foot ringworm did not seem to be of significance in this series. Although in half of all the cases (25 men, 26 women) some eczema appeared elsewhere on the body, it was in only 11 men and seven women that the feet were involved. In no case did the activity of foot tinea parallel the hand eruption.

Contact Dermatitis

These are cases in which external contact was accepted as virtually the sole cause of the eruption. The group contained eight men and four women.

In most of these cases a specific allergic sensitivity was demonstrated, but in three (one man and two women) the lesion was attributed to excessive exposure to strong cleansers and no allergic mechanism postulated. In one case, that of a female office-cleaner, a positive patch test to colophony was obtained and recovery followed avoidance of all floor and furniture polish, but the actual polish responsible was not identified. Within this group six of the male cases were occupational; in one woman the eruption was due to paid employment and in two to housework in their own homes.

Routine Patch Tests

In addition to patch tests with substances handled, and upon which the case history cast some suspicion, a series of tests were carried out as a routine, using a selection of possible allergens suggested by Professor C. D. Calnan (personal communication, 1961) (Table II).

TABLE II

Test Material	Positives	
	Expected	Unexpected
Formaldehyde 2% aqueous	—	—
Turpentine 5% in olive oil	—	1
Mercury perchloride 0·1% aqueous	—	3
Nickel sulphate 5% aqueous	6	2
Potassium bichromate 0·5% aqueous	1	3
Dipentamethylene thiuram disulphide 1% in soft paraffin	—	—
Mercaptobenzthiazole 1% in ung. emulsificans	—	—
Colophony 50% in soft paraffin	—	1
Balsam of Peru 25% in lanolin	—	2
Paraphenylenediamine 2% in soft paraffin	—	—
Salicylic acid 5% in eucerin	—	2
Primula leaf	—	1
Shampoo	1	
Photographic solutions	2	
Adhesive paste	1	

Fifteen unexpected positive results were obtained in the 84 patients thus tested, excluding those in whom the history led to the discovery of the allergen or suggested the need for a particular test.

In two cases of sensitivity to balsam of Peru, positive tests were afterwards obtained with orange-peel. Both patients peeled and ate oranges several times weekly and both recovered when they ceased to do so. This diagnosis would probably not have been reached had not a positive patch test unexpectedly appeared. Similarly, the identification of floor polish as the likely cause would probably not have been made had not an unexpected test reaction to colophony been obtained in the office cleaner already mentioned. Apart from these, the allergen unexpectedly revealed by these routine tests did not appear to be directly related to the present eruption, or even in most cases to have caused a previous dermatitis in these subjects.

While, therefore, the elucidation of these three cases was most pleasing, it seems doubtful whether this type of routine testing sufficiently repays the considerable effort it requires. In the Finsen Institute, Copenhagen, it has been standard practice for many years and has recently been reviewed by Hjorth (1963). In recording a large series of positive findings he mentions that of 445 cases 192 (43%) were deemed to be relevant to the eczema under investigation.

Occupational Eczema

In addition to the six cases of eczema due to work contacts, a further five men were considered to have an important occupational factor. Three of these worked as cleaners, and their exposure to detergents was probably relevant. Another, a police constable, was considerably exposed to detergents in washing his car. Finally, a baker developed hand eczema in circumstances suggesting occupational dermatitis, but the precise causative factor was never identified. This makes a total of 11 accepted cases of occupational dermatitis in men.

In addition to the four women with contact eczema, there were four more whose housework seemed to be a significant factor; one of these was a post-partum case.

Of the seven women who were occupational cases, four were engaged only in their own housework and the other three were employed in cleaning or domestic paid work as well. The

relative importance of their housework compared with their paid employment was naturally very difficult to assess.

Thus occupational dermatitis accounted for 18 cases, 17% of the total.

These figures are, of course, dependent upon a critical assessment of the occupational factor. When specific allergy can be shown and exposure to the allergen at work is known, the diagnosis is not usually in doubt; but when primary irritants are in question allergic sensitivity is not usual. Patch tests are of no value. The diagnosis then rests upon a history of a degree of exposure which constituted a notable risk, with recovery within a reasonable period—usually a few months—after exposure ceased. Delay in recovery can sometimes be explained by the intervention of other factors, such as infection or emotional upset, but more often it indicates that the causative factors were, in the first instance, incorrectly assessed and that work was not a significant component.

Psychiatric Factors

The aggravation of eczema by emotional or psychiatric factors is a familiar concept, though the extent to which this occurs is debatable. Anxiety and hostility are the symptoms most often regarded as relevant. MacKenna (1961) in respect of discoid eczema refers particularly to a stress reaction of the emotionally overburdened. In the present series only seven men claimed this association, but 20 women did so. These assessments were largely at the patients' own valuation and cannot be unquestionably accepted. In several cases where relapses were attributed to anxiety or to emotional stress it was possible to demonstrate to the patient, as it was with water and cleansers, that this explanation of the fluctuations in severity which they had supposed could not be verified by critical observation.

It was not possible to make an expert psychiatric assessment of all cases, but 20 patients, selected at random, were examined by Dr. G. F. Heseltine and compared with 20 matched patients who had eczema without hand involvement. Heseltine's (1963) results are striking. He recorded a frequent first onset after emotional stress equally in both groups and found also that the mother was the only or the dominant parent. More remarkable was a personality trait clearly brought out by Fould's intro-extra-punitive questionary. From this it emerged that eczema patients without hand involvement had a "criticism of others" rating significantly higher than those with hand eczema. Since this personality trait is present in early life, it is tempting to suppose that it is a factor which determines in an eczematous subject whether the lesions will involve the hands or appear on other parts of the body.

The effect of psychotherapy and of psychotropic drugs was not studied.

Effect of Water and Cleansers

The effect of water with soap and other cleansers on hand eczema has been very variously assessed by different observers. Sulzberger and Baer (1948), for example, gave great prominence to soap and cleansers as predisposing, precipitating, or aggravating factors in hand eczema. Gross (1959), on the other hand, regards all housewives' eczema as variants of nummular eczema, soap and similar substances being possible aggravators.

This is perhaps mainly a question of emphasis. Most writers accept the existence of an underlying personal predisposition which allows one person's skin to withstand, and another's to break down under, the attack of identifiable insults; they recognize, also, that factors such as exposure to soap and water are capable, at least in some circumstances, of aggravating, if not initiating, an eczematous process. It is over the relative importance of these aetiological ingredients that so much divergence of opinion exists.

Since soap and most cleansers are capable of showing primary irritant properties, it would not be surprising if they exerted some aggravating effect on any eczematous eruption, however this originally arose. But it is essential in this connexion to recall that many observations, notably those of Suskind *et al.* (1963), have failed to show aggravation of hand eczema by soap and cleansers when this has been tested under controlled conditions in the laboratory.

The ordinary use of soap for washing is brief and may be comparatively infrequent, so that the actual course of the disorder is not notably affected. Among the men in this series, 40 (over two-thirds) did not notice any apparent aggravation from washing. In five men whose work led to considerable exposure to water and cleansers, this factor was deemed important. In a further 10 men the use of water and cleansers led to some discomfort or itching, but did not appear to alter the course of the disease. In women, who are usually more exposed to water in the course of housework, 23 (including 10 housewives) were indifferent to water and cleansers; 11 (including eight housewives) were accepted as notably affected, and a further 15 (including 12 housewives) complained, though unconvincingly, that water and detergents made their eczema worse.

The idea that water, soap, and other cleansers may lead to dermatitis is prominent in the minds of housewives, but in several cases this belief could not be substantiated by critical observation. It is not often possible to observe the effect of completely stopping work in housewives. Rubber gloves may themselves aggravate the eczema, even though rubber allergy is not present. It was, however, often possible to observe considerable fluctuations in severity of the eruption which were quite independent of changes in housework, and the impression grew that the aggravating effects of wet work could not be confirmed.

It was formerly thought that soapless cleansers are more likely than soap to cause skin irritation. These detergents, however, differ so radically one from the other that any generalization is unlikely to be true. Indeed, many dermatologists tend now to the view that some soapless cleansers may be less likely to injure the skin than soap. In the present series housewives did not support the notion that soap is any less harmful, but the idea dies hard.

During the observation period an opportunity occurred to assess the value of a non-soap cleanser, Sevana, for ordinary toilet use. Wilkinson (1962) found that among patients with eczema Sevana was beneficial to one-third and inocuous in the great majority. In the present series the findings were comparable, but not clear-cut. The impression gained was that when irritation from soap was a source of complaint the use of Sevana for washing was often found preferable, more comfortable. In no case where Sevana was tried did it seem to make the eruption worse.

Idiopathic Cases

There remained 21 men and 20 women in whom causative or contributory factors baffled all recognition or were assessed as of negligible importance. The clinical appearance was usually of a patchy eruption, the detailed distribution of which did not recall any likely external factor. Observation over weeks and months showed fluctuations in severity which could not be related to the use of the hands or, in fact, to any other factor. Improvement under treatment was often fairly consistent, but there were cases where even this was unpredictable from one time to another. In objective clinical appearance the distinction between these cases and those accepted as occupational was often difficult to draw, and the history and observed course of the lesions were all-important in making the diagnosis.

An idiopathic hand eczema in a woman is often labelled housewives' dermatitis because these patients are so often house-

wives, and in a man it is termed industrial because he is a manual worker. But a large proportion of all women are housewives and a substantial proportion of all men work with their hands. In the present series, 12 of 20 women over 18 years of age were housewives ; this compares with 40% housewives in a random sample of general skin out-patients. Similarly, of 21 men nine had some kind of manual work, compared with 51% of all out-patients. These figures do not suggest that manual work or housework are likely to be important factors in these idiopathic cases.

In the present assessment idiopathic eczema constitutes 43% of the whole series, and some of the cases put in other groups —for example, the Sutton type, the psychosomatic cases—are clearly not occupational. If this is accepted, the important conclusion is that, in hand eczema in general, occupational dermatitis constitutes a minority and not, as is sometimes supposed, the bulk of the cases. The onus of proof should be to establish, not to exonerate, the occupational factor.

Among this idiopathic group an over-assessment of the degree of exposure to a primary irritant or of the extent and nature of emotional stress could sway the diagnosis to occupational dermatitis or to psychosomatic eczema, respectively ; the reverse process may, of course, take place. This is presumably a reason why some dermatologists diagnose industrial dermatitis or psychosomatic eczema so much more often than others, the diagnosis depending not only upon knowledge and experience but also upon the subconscious and ingrained emotional attitudes of the dermatologist himself. It is with this reservation that the diagnostic breakdown of the present series is recorded.

Diagnosis

The recognition that a hand eruption is eczematous presents no great difficulty. The diagnostic problem arises in assessing the causative factors. Two considerations arise: the nature and degree of a causal agent ; and its relevance to the case.

The nature and extent of a causal factor can be most difficult to judge. This may require, for example, an expert psychiatric assessment, or a visit to a factory to observe at first hand the degree of exposure of the skin to an irritant. A common mistake is to accept gross exposure to a non-irritant substance as a cause of industrial dermatitis.

Even when an acceptable aetiological factor has been recognized to be present in such a degree or extent as to be a fully possible cause, one still cannot without more evidence attribute the eruption to this, either alone or in part. Many people are exposed to possible causes of disease without becoming affected.

The relevance of a causative factor can be assessed by clinical examination in only a limited sense. It is often said that hand eczema due to external irritants involves chiefly the sides of the fingers, the webs, and the dorsa, and that eczema of psychosomatic origin is more likely to affect the palmar surfaces. The present series of cases has shown this criterion to be of limited value. Chief reliance has to be placed on the assumption that fluctuations in severity of the eruption will follow variations in the extent or degree to which a cause is operating and that elimination of the cause will be followed by recovery. If this sequence of events can be observed several times the probability increases. In this respect the history of onset and subsequent progress may be unreliable and the relevance of a causative factor be judged only after prolonged direct observation and, perhaps, experimentation.

Thus the course of the disease is most important and may, indeed, be the crucial factor in aetiological diagnosis. It is unfortunate that in industrial cases certification is required without delay for administrative reasons and a hasty diagnosis often has to be made on incomplete evidence before the relevance of possible causes has been observed or tested. This regrettable situation imposes an impossible task on the physician and gives rise to social injustice, of which the patient bears the chief burden.

Miss X, in the present series, developed hand eczema while handling photographic chemicals and was quite sure that these were responsible ; at first this seemed plausible, but patch tests were negative and her eruption was quite unaltered by a change of work. She then maintained that her eczema was psychogenic and produced a long written history showing, in retrospect, how her relapses had followed emotional upset. However, assessment by a psychiatrist did not reveal any abnormal psychiatric situation, and in the ensuing months it was easy to see, and to convince the patient herself, that fluctuations in the rash did not follow emotional upset. She was then quite satisfied to accept her eczema as idiopathic.

It has been said that to identify a high proportion of contact eczema is a reflection of diagnostic skill ; but unless specific allergic sensitivity is involved it may be more true to say that a high proportion of idiopathic cases in which possible causative factors have been considered and rejected reflects a more thorough and critical observation.

In the present series of hand eczema it has seemed that in the great majority of patients the named causative factors are, at the most, aggravators and that the essential reason for the eczema remains obscure.

Treatment and Prognosis

Treatment was mainly, often entirely, with local applications. Zinc cream, with 2–3% liq. pic. carbon. or 2% ichthammol, was the most usual application, the hands being protected with thin cotton or nylon gloves. Only three men and five women were unresponsive to local treatment. In about half of all cases a steroid cream proved more efficient. In difficult cases the most effective treatment was with fluocinolone or triamcinolone acetonide applied at night, the hands being occluded in thin polythene gloves.

Recovery quickly followed in most cases where a specific contact allergen could be identified and eliminated. The anomalous situation regarding nickel sensitivity, where the eruption persists in spite of the elimination of contact, has already been mentioned. The same was seen in two patients who were unexpectedly found to be sensitive to chromium. In non-allergic occupational cases recovery was less certain. In all, 13 occupational cases recovered in an average total duration of 19 months, including the period before diagnosis was made. On an average, these patients had their eruption for 10 months before attending hospital ; thus they were nine months under investigation and treatment before complete recovery.

The best results were in the nummular type, 8 out of 16 recovering in an average total period of 13 months (seven months under treatment).

Of the idiopathic cases, nearly half (19 out of 41) recovered in an average of 28 months (14 months' treatment).

The worst group were of the Sutton type, one recovery being that of the man found to have a specific allergy to balsam of Peru and orange-peel, the other that of a woman who was clear after two years. The remainder improved while treatment continued, but relapsed within a few days when local applications were interrupted.

Summary and Conclusions

The close and prolonged clinical observation of 106 cases of hand eczema is recorded. Clinical types are defined.

In 39% no significant causative factor could be found.

In many cases where causative factors could be identified, these were probably no more than contributory, superimposed upon an underlying idiopathic eczema.

Seventeen per cent. of cases were thought to be occupational.

In the diagnosis of industrial dermatitis the course of the illness, especially in relation to changes in work, is often of decisive importance.

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Further Serological Studies on the Rubella Syndrome

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A number of protozoal, bacterial, and viral infections contracted in pregnancy may give rise to foetal damage which becomes manifest either by abortion, stillbirth, a chronic sublethal infection recognizable after birth, or by teratogenic effect. The exact nature of the risk of foetal damage following infection is hard to assess except in the case of rubella. This relationship was first noted by Gregg (1941) and later by Swan (1944), who drew attention to malformation of the eyes and hearing-organs after maternal rubella in the first trimester. The detailed prospective studies of Lundström (1952, 1962) in Sweden and Manson *et al.* (1960) in England provided the necessary data for evaluation of this risk. Apart from a slightly higher incidence of stillbirths and infant deaths, the main effects noted were cataracts, deafness, and congenital heart disease, particularly patent ductus arteriosus, microcephaly, and coexistent mental retardation. These defects, occurring either singly or in combination, are referred to collectively as the rubella syndrome. In Lundström's series 1,146 pregnant women exposed to rubella were studied. The incidence of the rubella syndrome was 11%, 11%, and 8% for each of the first three months respectively, with an overall incidence of 10% for the first trimester. The figures of Manson *et al.* for the same stages of pregnancy were 15.6, 19.7, and 13.0%, and an overall figure of 15.8% for the first trimester. The figures for the second trimester from these two series were 0.9% and 2.6% respectively. Other prospective studies quoted by Lundström (1962) have shown wide variation and generally higher figures. However, in the light of present knowledge figures of Lundström and Manson *et al.* have received general acceptance, and there is general agreement that the highest incidence is in the first trimester.

The teratogenic effect of rubella on the human foetus is the reason for studying this otherwise mild infectious disease. The recent discovery, by several groups in North America, that the virus could be grown in cell culture opened up a new approach to the study of rubella and of the mechanism producing foetal damage. The first point studied was the serological status of children with the rubella syndrome. It was shown by Plotkin *et al.* (1963) that 8 out of 11 such children aged 5 months to 10 years had neutralizing antibody titres to rubella virus—six in high titre, two in titres of 4—and three children had no demonstrable antibody. The question that naturally arose from these findings was whether this antibody represented residual maternal antibody or whether it was actively produced. There seemed to be no reason why maternal antibody should persist for a longer period in rubella than in any other virus disease in which antibody passively transferred across the placenta disappears during the first six months of life. These results suggested, therefore, that antibody had been actively produced and that the foetus exposed to rubella-virus antigen *in utero* is not rendered immunologically tolerant. These sera were tested for neutralizing antibody by means of the interference-inhibition test in vervet-monkey-kidney cells as described by Parkman *et al.* (1962). Recently McCarthy *et al.* (1963) described an alternative method of measuring rubella-neutralizing antibody in a continuous line of rabbit-kidney cells, the RK-13 line, in which rubella virus produces a cytopathic effect. We have found this to be a more convenient and reliable method for antibody estimation, and the results here reported have been obtained by this method. The present study reports our findings on a number of children with the rubella syndrome compared with control groups. It was carried out with the object of determining whether the foetus exposed to rubella virus was capable of developing an active immune response to the infection occurring in foetal life.

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Material and Methods

The cases under investigation were divided into two main groups. *Group A : the rubella group ;* children with the rubella syndrome and children exposed to intrauterine rubella infection. *Group B : the control group.*

Group A : The Rubella Group

Series I.—This consisted of 14 children with the rubella syndrome, whose ages ranged from 4 months to 10 years, from whom a single sample of serum was collected. Five of these children were included in our previous report on the rubella syndrome (Plotkin *et al.*, 1963).

Series II.—From each of 17 children with the rubella syndrome and their mothers serum specimens were obtained concurrently. In this group the diagnosis of rubella syndrome was checked with the hospital records. A history of maternal rubella was forthcoming in every case ; contact rubella infection with a member of the family was reported in seven cases ; none of the mothers was given gamma-globulin after exposure.

Series III.—These six children were exposed to maternal rubella in the first trimester, but were without clinical evidence of rubella syndrome when examined at 6 months of age.